REVIEW

Respiratory involvement in inherited primary muscle conditions

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Patients with inherited muscle disorders can develop respiratory muscle weakness leading to ventilatory failure. Predicting the extent of respiratory involvement in the different types of inherited muscle disorders is important, as it allows clinicians to impart prognostic information and offers an opportunity for early interventional management strategies. The approach to respiratory assessment in patients with muscle disorders, the current knowledge of respiratory impairment in different muscle disorders and advice on the management of respiratory complications are summarised.

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In primary muscle disorders, the main cause of morbidity and mortality is the involvement of respiratory muscles, which leads to ventilatory failure. Certain muscle conditions, such as congenital muscular dystrophy (MDC), infant-onset nemaline myopathy and myotubular myopathy, are associated with early respiratory muscle involvement; most of these patients do not survive past early childhood. In other conditions—for example, Duchenne muscular dystrophy—respiratory involvement occurs in the teenage years, often at a time when care is being transferred from paediatric to adult services. With advances in diagnostic techniques, the number of muscle disorders in which the onset of respiratory failure in adulthood has been described is steadily increasing.

Knowledge of the respiratory complications of muscle disorders is therefore essential for paediatricians and adult physicians, both in neurology and respiratory medicine. Early intervention can be instituted to improve patient well-being and survival. This review provides guidance on the evaluation of respiratory function in patients with muscle disorders, summarises the degree of respiratory involvement in the various inherited primary muscle disorders and finally gives advice on the management of patients in respiratory failure.

RESPIRATORY EVALUATION IN MUSCLE DISORDERS

Symptoms

Symptoms caused by respiratory failure may be specific, such as breathlessness, or more general, such as fatigue, lethargy, poor appetite, weight loss and impaired concentration. Patients may describe breathlessness at rest or on exertion, depending on the severity of the muscle weakness. With the association of the diaphragm, symptoms of orthopnoea or breathlessness may be apparent when bending over. Breathlessness experienced when a person is immersed in water above the waist—for example, when entering a swimming pool—is a rare but classical symptom of diaphragm weakness.

When the upper airway musculature is affected, speech and swallowing difficulties start to develop. Snoring, apnoeic episodes and daytime somnolence point to the possibility of obstructive sleep apnoea. If patients underventilate at night, the resultant hypercapnia may cause early-morning headaches, reduced concentration or clouded consciousness. Blurring of vision from papilloedema has been described, but is rare and only seen in severe hypercapnia.

A history of recurrent chest infections may indicate an ineffective cough. Coughing requires activation of the inspiratory muscles, closure of the glottis and then contraction of the expiratory muscles, particularly those of the abdominal wall; finally, the expulsive phase is initiated by opening the glottis. A poor cough can result from weakness or in-coordinated contraction of the inspiratory, glottic or expiratory muscles.

Clinical signs

The classic flapping tremor of hypercapnic respiratory failure is a late sign, as is central cyanosis. Signs of right heart failure may be present if the patient is chronically hypoxic.

Patients with respiratory muscle weakness may have a rapid, shallow breathing pattern, the aim of which is to lower the elastic work per breath.[1] As well as timing the respiratory rate, it is important to observe which muscles are being used during tidal breathing. Abdominal paradox, during which the abdominal wall moves inwards with inspiration, suggests diaphragmatic weakness.[2] Ribcage paradox, in which the ribcage moves inwards during inspiration, indicates intercostal muscle paralysis. Recruitment of accessory neck muscles during tidal breathing implies severe weakness of the main respiratory muscles.

Abbreviations: AMD, acid maltase deficiency; DM1, myotonic dystrophy; DM2, proximal myotonic myopathy; DMD, dystrophinopathy; EDMD, Emery–Dreifuss muscular dystrophy; EDS, excessive daytime sleepiness; FRC, functional residual capacity; FSH, facioscapulohumeral dystrophy; FVC, forced vital capacity; LGMD, limb-girdle muscular dystrophy; MDC, congenital muscular dystrophy; MIP, maximal inspiratory mouth pressure; NIV, non-invasive invasive ventilation; $PaCO_2$, arterial carbon dioxide tension; SNIP, sniff nasal inspiratory pressure; SpO_2, single oxygen saturation

The patient should be asked to take deep breaths in and out, to give an idea of the difference between tidal volume and vital capacity. This gives an indication of the amount of respiratory reserve, but is less informative than observing tidal respiration. The observer should be aware that patients can mimic chest expansion by flexion and extension of the spine.

Simple bedside observation of a cough and a sniff gives a surprisingly accurate estimation of the strength of the inspiratory and expiratory muscles.

A full neurological examination to assess respiratory muscle weakness is mandatory to ascertain the underlying diagnosis.

Investigations

Vital capacity is one of the most reproducible tests of lung function. It is insensitive to the early stages of respiratory muscle weakness, as it may not fall below normal limits until there is a 50% reduction in muscle strength,[3] but clinically relevant weakness is unlikely if the vital capacity is normal. Serial measurements of vital capacity are helpful for monitoring respiratory muscle function. Supine vital capacity measurements can be used to detect diaphragmatic weakness, which is indicated by a fall of 15% or more in vital capacity from the sitting to the lying position.[4]

Muscle weakness produces a restrictive pattern on spirometry, with the forced expiratory volume in 1 s being reduced to a similar extent to vital capacity. The ratio of forced expiratory volume in 1 s to vital capacity is therefore normal or high. If forced vital capacity (FVC) is measured in addition to relaxed vital capacity, the larger of the two should be used.

It is seldom helpful to measure other lung volumes in muscle disease. Total lung capacity will be low as a consequence of weak inspiratory muscles and the stiffness of the lungs and chest wall that develops in longstanding respiratory muscle weakness. The exact mechanism of this stiffness remains unclear. Functional residual capacity (FRC) is at the relaxed point of the thorax, which should not be influenced by respiratory muscle strength; in chronic weakness, it may be low if the lungs are stiff. Expiratory muscle weakness impairs the ability to deflate the ribcage below FRC, so residual volume may be higher than expected. Gas transfer shows the characteristic pattern of extra-pulmonary restriction with a low TLCO (transfer factor for carbon monoxide) but high KCO (coefficient for carbon monoxide). In severe respiratory muscle weakness, flow during forced expiration may be limited by the strength of the expiratory muscles rather than by airway collapse; the result is a characteristic abrupt cessation of flow as the patient reaches residual volume, rather than the usual tail of low flow as airways collapse.

Maximal inspiratory mouth pressure (MIP) is measured during a maximal, static inspiratory effort from either FRC or residual volume. Maximal expiratory pressure is measured during a maximal expiratory effort from either FRC or total lung capacity. The lips form a tight seal around a large-diameter mouthpiece, usually in the form of a flange. The nature of these measurements is such that a high or normal mouth pressure should exclude clinically relevant respiratory muscle weakness, but a low value may reflect poor effort or difficulty in obtaining a good seal with the mouthpiece and true muscle weakness. Several normal ranges for maximum mouth pressures have been published, but values >80 cm H_2O exclude clinically relevant respiratory muscle weakness. A low MIP with a normal maximal expiratory pressure can be a pointer to the presence of a problem in the diaphragm.[5]

Sniff nasal inspiratory pressure (SNIP) is a more natural manoeuvre, which some patients find easier than MIP.[6–8] If MIP is low, SNIP should be recorded and the higher of the two values should be used. A pressure of 80 cm H_2O can also conveniently be used as the lower limit of normal for SNIP. Expiratory muscle action can be assessed by peak expiratory cough flow rate, provided bulbar function is intact.[9] A peak expiratory cough flow rate of >270 l/min is required to produce an adequate cough.[10]

Measurement of trans-diaphragmatic pressure includes placement of pressure transducers, catheters or balloons in the stomach and oesophagus. This excludes the influence of upper airway musculature and allows a more accurate partitioning of respiratory muscle involvement. Stimulation of the phrenic nerves, electrically or magnetically, overcomes the volitional aspect of all other respiratory muscle tests and permits the calculation of phrenic nerve conduction time.[11 12]

Failure of the respiratory muscles to maintain normal alveolar ventilation leads to an increase in the arterial carbon dioxide level (arterial carbon dioxide tension ($PaCO_2$)). This may be measured using an arterial or arterialised capillary sample. Non-invasive carbon dioxide tension analysers show good agreement with arterial data. If anything, they tend to give a slightly higher value of $PaCO_2$, so a normal non-invasive reading can usually be taken as good evidence that the patient is not in hypercapnic respiratory failure. Patients will try to maintain a normal $PaCO_2$ for as long as possible; an increased $PaCO_2$ is a very late development, indicating that the respiratory muscles have reached a critical stage of weakness that requires urgent intervention. A single oxygen saturation (saturation pressure of oxygen (SpO_2)) reading is only really useful if the result is low, indicating the need for arterial blood gas sampling; severe hypercapnia is, however, unlikely if the SpO_2 is $\geqslant$94% while the patient is breathing room air.

Before the development of daytime hypercapnia, patients will go through a phase where the $PaCO_2$ is increased during the night but is normal during the day. An increase in the bicarbonate in a daytime blood gas sample should alert the clinician to the possibility of nocturnal hypoventilation. An early-morning arterial sample is sometimes advocated, but overnight monitoring of gas exchange is more appropriate. The parameters recorded will depend on the local availability of equipment and expertise. Oxygen saturation monitors are widely available and they are easy for the patient to use at home. Although they can be criticised for not directly measuring ventilation, in practice, severe hypercapnia is unlikely if the oxygen saturation remains normal throughout the night, provided the patient is not breathing supplementary oxygen. If overnight oximetry is abnormal or if the clinical suspicion of nocturnal hypoventilation is high despite normal oximetry, transcutaneous carbon dioxide monitoring can be undertaken. This is used routinely in some centres. Additional parameters can be added to monitoring during sleep, depending on the clinical question to be answered. The term polysomnography usually implies inclusion of electroencephalography.

Radiographic and ultrasound imaging of the diaphragms during sniffing can be used to assess diaphragm motion, but they are poorly reproducible and seldom clinically informative.[5]

PRIMARY MUSCLE DISORDERS AND THEIR EFFECT ON RESPIRATION

Dystrophinopathy

Duchenne muscular dystrophy (DMD) has an X-linked recessive pattern of inheritance and affects up to 1 in 3300 live male births.[13] Affected toddlers exhibit a delay in motor skills, but by the age of 10–12 years most patients with DMD typically become wheelchair dependent.

The typical respiratory progression of patients with DMD is seen in an increase in vital capacity as predicted until about 10 years of age, after which it plateaus. With the development of respiratory muscle weakness and skeletal deformities, vital capacity starts to fall.[14] The rate at which vital capacity declines is around 8% per year.[15] Serial measurement of vital capacity can monitor the progression of respiratory involvement. Vital capacity <1 l has been shown to be a reliable surrogate marker of mortality with a 5-year survival of 8%.[16] Historically, life expectancy in DMD was short (in the 20s), but recent studies have shown that non-invasive invasive ventilation (NIV) can increase the median survival of patients with DMD.[17 18] A recent study has also shown that although patients with DMD are severely disabled, they still perceive a high quality of life, which appears to be unrelated to their physical disability or respiratory impairment.[19]

Becker muscular dystrophy has characteristics similar to DMD but with a milder phenotype. Similar mutations occur in the dystrophin gene at chromosome Xp21, with a reduction, as opposed to an absence, of dystrophin.[20] Patients have a symmetrical proximal muscle weakness with associated wasting and there is cardiac involvement, which can precede skeletal weakness. The progression of the condition is less predictable and patients can remain asymptomatic until their 60s.[21 22] Respiratory involvement is not typical but can occur, and lung function should be monitored at annual intervals.

Myotonic dystrophy

Myotonic dystrophy (DM1) is the most common muscular dystrophy in the adult population and has an incidence of 1 in 8000. It is a multisystem disorder and inheritance occurs in an autosomal dominant manner. The condition is caused by an unstable trinucleotide expansion at chromosome 19q13. The typical clinical presentation is with bilateral facial weakness, ptosis and distal weakness with evidence of myotonia.[23] The main cause of morbidity and mortality, however, is cardiac and respiratory involvement. It is important to recognise this early, as the heart and lungs can be affected even when muscular symptoms are mild.

In proximal myotonic myopathy (DM2), despite similar clinical characteristics, patients do not display an abnormal cytosine–thymidine–guanine expansion. A linkage to chromosome 3q has been established.[24 25] The clinical spectrum in proximal myotonic myopathy is variable, but weakness is usually in a more proximal distribution and muscle pain is more prominent than in DM1.[25]

Respiratory impairment in DM1 can present in several ways. The most frequent presentation is excessive daytime sleepiness (EDS), which can occur in the absence of respiratory failure.[26 27] The exact cause of EDS in DM remains unclear, but studies have suggested a primary central nervous system dysfunction of sleep regulation.[28 29] EDS can be particularly disabling for patients, as it can affect quality of life.[27] Modafinil, a central nervous system stimulant, has been shown to help reduce hypersomnolence and improve mood in patients with DM1.[30 31]

Alveolar hypoventilation is an important complication in DM1, which results from a combination of respiratory muscle weakness and dysfunction of the respiratory centres in the brain.[32–35] NIV can improve symptoms and survival in patients with DM1, but most patients are unable to tolerate the mask and adherence to this treatment is poor.[26] Routine monitoring of respiratory function is of limited value in this group of patients.

Patients with DM1 are at risk of aspiration pneumonia due to failure of pharyngo-oesophageal muscle function.[36] They may also exhibit weakness and myotonia of the respiratory muscles.[37 38] A study on mortality in a cohort of patients with DM found pneumonia to be the most common underlying factor.[39]

Other potential hazards in DM1 include perioperative pulmonary complications encountered with anaesthesia: acute respiratory failure, cyanosis, atelectasis and pneumonia. The risk is increased in older patients with DM1, who have more severe muscle weakness, and in those undergoing abdominal surgery.[40] There have been reports of certain anaesthetic agents such as thiopentone, halothane and suxamethonium precipitating respiratory complications. This is now thought to be due to the depressant effect of the drugs rather than a specific sensitivity to the agent.[23 41]

Facioscapulohumeral dystrophy

Facioscapulohumeral dystrophy (FSH) is predominantly inherited in an autosomal dominant pattern, with sporadic mutations accounting for the remaining cases. The prevalence of FSH is 1 in 20 000. The clinical manifestations are heterogeneous, but patients typically present in the second decade. The diagnosis is supported by genetic confirmation in most cases.[42–44]

The typical clinical features of FSH are muscular weakness associated with facial, scapular fixator, bicep, finger, dorsiflexor, abdominal, and hip-girdle and foot extensor muscles. Extraocular, bulbar and respiratory muscles tend to be spared. Cardiac involvement can occur, typically manifesting with conduction defects or arrythmias.[45 46] Disease progression is usually slow, although about 20% of cases become wheelchair dependent.

Respiratory evaluation in patients with FSH can prove difficult, owing to facial weakness causing poor mouth seal. Spirometry values may be less accurate and mouth pressures are unreliable. Clinical assessment of respiratory impairment is essential, coupled with arterial blood gas analysis. A recent study of respiratory insufficiency in the Dutch population with FSH suggested that about 1% of patients required ventilatory support. This was associated with severe disease, wheelchair dependence and kyphoscoliosis.[47]

Limb-girdle muscular dystrophy

Limb-girdle muscular dystrophies (LGMDs) are divided into two groups: autosomal dominant (LGMD 1) and autosomal recessive (LGMD 2). The letters suffixed correspond to the chronological order in which each genetic locus was discovered.[48]

LGMD 1 is rare, accounting for 10% of the total number of LGMD cases. Presenting clinical features suggestive of an autosomal dominant muscular dystrophy include a positive family history, a relatively low creatine kinase, early development of contractures and the presence of a cardiac conduction block.[49] Little evidence exists in the literature regarding respiratory involvement in LGMD 1. However, with the development of contractures, scoliosis and spinal rigidity may occur, causing a restrictive pattern of respiratory impairment. An example of this is LGMD 1B, where the genetic mutation has been mapped to chromosome 1q, which alters the lamin A/C protein, a defect also present in Emery–Dreifuss muscular dystrophy (EDMD), making the two conditions allelic.[50] As in EDMD, spinal rigidity can lead to restrictive respiratory impairment and should therefore be closely monitored.

LGMD 2 accounts for 90% of cases and is inherited in an autosomal recessive manner. Many different subtypes have been described. The sarcoglycanopathies (LGMD 2C–2F) present in a fashion similar to the dystrophinopathies.[51] A recent evaluation of respiratory involvement in sarcoglycanopathy suggested that more than 70% of cases have respiratory muscle involvement with reduced FVC. γ and α sarcoglycanopathy were observed to have severe respiratory insufficiency, with FVC reduced to <40% predicted.[52] In calpainopathy or LGMD 2A, there is late respiratory muscle involvement with sparing of the cardiac muscles.[53 54] Presentation with cardiorespiratory failure has been reported after an acute respiratory tract infection, but is a rare occurrence.[55]

LGMD 2I is associated with mutations in the fukutin-related protein gene. Patients typically present in adulthood with proximal limb muscle weakness. Respiratory muscle weakness—in particular, diaphragmatic weakness—is often observed. This can occur even in ambulant patients. Serial measurements of vital capacity will show a gradual deterioration, initially causing symptoms of nocturnal hypoventilation before the development of respiratory failure.[56]

Emery–Dreifuss muscular dystrophy

EDMD is a genetically heterogeneous condition with features of early contractures, progressive humeroperoneal muscle weakness and cardiac conduction block.[57 58] The main morbidity associated with this condition is a life-threatening cardiac conduction block, which can be managed by the insertion of permanent pacemakers. Patients with EDMD develop scoliosis, contractures and spinal rigidity, leading up to a restrictive pattern of respiratory impairment.[59]

Oculopharyngeal muscular dystrophy

Oculopharyngeal muscular dystrophy is an inherited condition that can be dominantly or recessively inherited. The condition is caused by a stable trinucleotide repeat expansion at the poly-(A)-binding protein gene on chromosome 14q.[60] As well as bulbar weakness and progressive ptosis, patients can also have facial and proximal muscle weakness.[61] As a result of bulbar weakness, patients run the risk of developing aspiration pneumonia and obstructive sleep apnoea.[62] This is of particular importance to patients undergoing surgical procedures, where multiple intubations, tracheostomy and prolonged intensivecare may be required.[63]

Bethlem myopathy

Bethlem myopathy is an autosomal dominant inherited condition associated with early-onset myopathy with contractures.[64] Recent evidence has implicated collagen VI as the defective protein. The contractures typically affect the fingers, wrist, elbows and ankles. Patients tend not to find this disabling until later on in life.[65]

Respiratory involvement occurs and appears to be related to the severity of muscle involvement. Respiratory failure requiring ventilation has been reported at as early as 20 years of age and regular respiratory assessment is recommended in such patients.[66 67]

Metabolic myopathies

Metabolic myopathies represent a group of disorders with deficiencies in the metabolism of glycogen, fatty acids and mitochondria. Patients can present at an early age with hypotonia, progressive weakness and severe multiorgan failure. Presentation in adulthood typically occurs with exercise intolerance, muscular cramps and myoglobinuria.[68–70]

Glycotic or glycogenoses disorders are usually induced by brief high-intensity exertional activities, resulting in acute muscle breakdown. With rest, patients may go on to experience a ''second-wind phenomenon'', where exercise tolerance improves.[69] These disorders range from glycogenosis type I to XII, depending on the particular affected enzyme, and most follow an autosomal recessive pattern of inheritance. Of particular interest are type V or McArdle's disease and type II or acid maltase deficiency (AMD). McArdle's disease is caused by myophosphorylase deficiency and is typically manifested by exercise intolerance, muscle cramps, myoglobinuria, muscle swelling and weakness. Respiratory insufficiency resulting in death in infancy has also been described.[71 72] In AMD, the lysosomal α-glucosidase enzyme is affected.[73] In early life, this enzyme participates in mobilising glycogen from the liver. Later in life, the enzyme prevents glycogen storage in the lysosomes. The clinical severity of the condition is dependent on the level of activity of the enzyme. Three clinical syndromes of AMD have been described. In infantile Pompe's disease, hypotonia, weakness and organomegaly occur. Respiratory function is affected early and death occurs by about 2 years of age. The childhood and adult forms typically present with proximal and respiratory muscle weakness. Mechanical ventilation is usually required later as the disease progresses.[69] Presentation of adult AMD with respiratory failure and cor pulmonale has been reported.[74] Treatment is supportive, although enzyme replacement may become available in the near future.[75]

Defects in fatty acid metabolism are rare and the typical clinical pattern tends to be associated with periods of high-energy requirements or uptake, as is seen in fasting and after exercise. No reports of respiratory muscles being preferentially affected exist, although with severe rhabdomyolysis and muscle necrosis, respiratory failure can ensue.[69]

Mitochondrial disorders include chronic progressive external opthalmoplegia, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes, and myoclonic epilepsy and red-ragged fibres.[76–78] Any one of these conditions can cause a myopathy.[79] Respiratory involvement can be a result of respiratory muscle weakness, sometimes with minimal limb involvement.[74 80–85] Other causes that can give rise to respiratory difficulties include central hypoventilation as a result of severe encephalopathy or a hyperventilation syndrome after lactic acidosis.[86 87]

Congenital muscular dystrophies

MDCs are a group of autosomal recessive disorders presenting in the neonatal period. Infants are usually hypotonic at birth and progressive weakness ensues.

Respiratory involvement in patients with MDC is inevitable. At the severe end of the spectrum, including Fukuyama MDC, muscle–eye–brain disease and Walker–Warburg syndrome, early-onset mental retardation and severe progression of muscular weakness with respiratory failure are seen. Patients rarely survive past their early teens.[88–91] In Ullrich MDC and MDC with rigid spine syndrome, diaphragmatic weakness is a feature even when patients are still ambulant, necessitating early respiratory monitoring.[92 93] In MDC1A, MDC1B and MDC1C, a correlation between motor and respiratory function has been observed. Patients who are wheelchair dependent seem to have a severe restrictive ventilatory defect and marked nocturnal hypoventilation.[94]

Congenital myopathies

Congenital myopathies include nemaline myopathy, central core disease, minicore myopathy and myotubular myopathy. Respiratory involvement is inevitable in both myotubular myopathy and multicore myopathy, and rare in central core disease. X-linked myotubular myopathy has an onset in infancy and is associated with high mortality, neonatal hypotonia and severe respiratory insufficiency causing early death. Phenotypic variability and cases of recovery after initial neonatal asphyxiation have, however, been reported.[94–98]

Patients with multiminicore myopathy have associated respiratory involvement that can occur when they are still ambulant. In a study on 19 patients with minicore myopathy, respiratory failure was observed in more than half the patients over the age of 10 and this was found to correlate with the degree of scoliosis evident in these patients. Another report of three ambulant men with multicore myopathy showed evidence of nocturnal hypoventilation and reduced vital capacities, eventually leading to respiratory failure. Early intervention with non-invasive ventilation led to improvement of arterial blood gas parameters and of symptoms.[99 100]

In nemaline myopathy, the severity of respiratory involvement depends on the time of disease onset and clinical severity of the condition. Marked respiratory involvement requiring early ventilation has been described in severe neonatal cases.[101] In adult-onset nemaline myopathy, muscle weakness may present later in life; respiratory weakness has been known to occur when patients are still ambulatory and also as the initial presentation.[102]

Distal myopathy

Distal myopathy is uncommon and may be inherited or may occur as a sporadic mutation. The condition is characterised by progressive weakness starting in the distal limb muscles with associated myopathic changes on muscle biopsy. Examples of this group of myopathies include Laing myopathy, Welander distal myopathy and Markesbery–Griggs–Udd myopathy, which are autosomal dominant conditions, and Nonaka myopathy and Miyoshi myopathy, which are autosomal recessive.

Respiratory involvement is unusual in the distal myopathies. The exception is myofibrillar myopathy associated with an abnormal accumulation of desmin, which is associated with a poor prognosis.[103] Disease onset typically occurs in middle adulthood, with distal lower limb weakness progressing to other muscle groups, including facial, bulbar and respiratory muscles. Cardiac involvement is also frequent, resulting in eventual mortality.[104]

MANAGEMENT OF RESPIRATORY COMPLICATIONS IN MUSCLE CONDITIONS

Monitoring

Effective management of the respiratory complications of muscle conditions hinges on early detection. Arguably, all patients with a muscle condition should have their respiratory muscles assessed once, using vital capacity and mouth pressures. If the results are normal and if respiratory muscle involvement is unlikely, then further testing can be deferred until there is any clinical suspicion of respiratory problems; at this point, it is extremely useful to have a previous set of lung function test results for comparison. Patients with conditions where respiratory muscle involvement is well recognised should have spirometry annually. If their disease is rapidly progressive or if their vital capacity falls below 1.5 l, then it may be reasonable to test more frequently—for example, every 3–6 months.[16] Once the vital capacity is less than 1.5 l, SpO_2 and PCF should be added to the test routine.

Respiratory muscle training

A small number of trials on respiratory muscle training have been reported. In general, these have concentrated on respiratory muscle strength or endurance and shown some benefit.[105–108] It is unclear whether these changes result in clinical benefit—for example, delaying the onset of respiratory failure—but if so, the benefits are likely to be seen in patients with fairly early respiratory muscle involvement rather than in those on the brink of decompensation. Respiratory muscle training requires a high level of motivation from the patient.

Non-invasive ventilation

NIV in the form of intermittent positive pressure ventilation via a mask has now largely superseded other non-invasive methods of ventilatory support. It is associated with fewer complications—particularly pneumonia—than endotracheal intubation. It can be started at an earlier stage, before the patient is in an extreme condition, and can be used intermittently. Many patients with neuromuscular conditions use NIV only at night.

The question of when to start NIV remains controversial. Prophylactic use before the onset of respiratory failure has not been encouraged after the increased mortality seen in a study of NIV in patients with DMD.[109] At present, NIV is recommended in patients who have daytime hypercapnia ($PaCO_2 > 6$ kPa), on the basis that a respiratory crisis may be imminent.[110] Nocturnal NIV is indicated in patients with disturbed sleep and daytime sleepiness secondary to nocturnal hypoventilation. It can sometimes be difficult to decide whether daytime symptoms are related to nocturnal hypoventilation, particularly when this has developed over a long period, and a trial of NIV may be the best way of ascertaining this. Some evidence suggests that patients with asymptomatic nocturnal hypoventilation will deteriorate quite rapidly and require NIV within 1–2 years; some patients in this group may choose to start NIV before they are symptomatic.[111] Although criteria to define nocturnal hypoventilation have been published, they are entirely arbitrary and it is probably best to make decisions about NIV on an individual basis.

Invasive ventilation

Patients with muscle disorders may present with such severe respiratory failure that it is safer to intubate them than to use NIV. A trial of extubation, transferring to NIV, is preferable to tracheostomy. Some patients who become completely dependent on NIV choose to be ventilated long term via a tracheostomy, and this may be the only option open to patients with bulbar problems or severe facial muscle weakness in whom NIV is ineffective.

Assisted coughing techniques

A resurgence of interest in mechanical cough-assist devices has been observed, but simpler methods of improving cough, such as manual compression, glossopharyngeal (frog) breathing and insufflation using a self-inflating resuscitation bag, should not be neglected. These measures can be used at home or by physiotherapists in hospital in the event of a respiratory tract infection.[112–115]

Other measures

Most respiratory crises are precipitated by a respiratory tract infection. Pneumococcal and influenza vaccination should be recommended. Patients should keep a prescription for antibiotics at home, and be advised to start them as soon as they start to feel chesty. In patients with bulbar problems, speech and language therapists will be able to offer advice about measures to reduce the risk of aspiration.

CONCLUSIONS

Respiratory dysfunction can be an important cause of morbidity and mortality in inherited muscle disorders. We have summarised the degree of respiratory involvement in various inherited primary muscle conditions (table 1).

Respiratory failure is inevitable in patients with DMD, MDC and certain congenital myopathies such as myotubular myopathy and minicore myopathy. In conditions such as myotonic dystrophy, AMD, limb-girdle muscular dystrophy, nemaline myopathy and Bethlem myopathy, respiratory failure can be the initial presenting feature, at times while the patient is still ambulant. In other conditions, namely FSH and Becker muscular dystrophy, the progression of the disease is associated with gradual loss of respiratory muscle strength. Spinal rigidity and scoliosis are associated with respiratory impairment and are features in patients with EDMD, merosin-positive MDC and LGMD 1. Awareness of the patients at risk is important, as respiratory failure can be reversed with the correct treatment.

Little evidence exists to suggest the timing of respiratory assessment, but if patients were at least assessed at their

Table 1 Degree of respiratory involvement in various inherited primary muscle conditions

Condition	Respiratory involvement
Duchenne muscular dystrophy	Inevitable, usually in teens, due to respiratory weakness
BMD	Less known but can occur with disease progression
DM1	Common, due to Sleep disordered breathing Respiratory muscle weakness and myotonia Alveolar hypoventilation Aspiration pneumonia
FSH	Respiratory insufficiency reported in severe disease
LGMD 1	Can occur due to scoliosis and spinal rigidity
LGMD 2	
LGMD 2A (calpainopathy)	Late involvement
LGMD 2B (dysferlinopathy)	Not reported
LGMD 2C (γ sarcoglycanopathy)	Common
LGMD 2D (α sarcoglycanopathy)	Common
LGMD 2E (β sarcoglycanopathy)	Common
LGMD 2F (δ sarcoglycanopathy)	Common
LGMD 2G	Not reported
LGMD 2H	Not reported
LGMD 2I	Common
EDMD	Occurs in association with skeletal deformities
OPMD	Aspiration pneumonia and sleep disordered breathing reported
Bethlem myopathy	Common
Autosomal dominant DM	
Laing	Rare
Welander	
Markesbery–Griggs–Udd	
Autosomal recessive DM	
Nonaka	Rare
Miyoshi	
Myofibrillar myopathy with abnormal desmin	Common
Metabolic myopathy	
Glycogenosis type II (AMD)	
Infantile	Common
Childhood/adults	Common
Glycogenosis type V (McArdle's)	Respiratory failure with acidosis reported
Fatty acid metabolism disorder	Uncommon unless severe rhabdomyolysis
Mitochondrial disorders	Can present with Respiratory muscle weakness Hyperventilation syndrome secondary to acidosis Central hypoventilation
Congenital myopathy	
Nemaline myopathy	
Infantile/childhood	Inevitable
Adult	Common
Central core disease	Rare
Minicore myopathy	Inevitable
Myotubular myopathy	Inevitable
MDC	
Normal cognition, merosin negative	
MDC 1A, 1B, 1C	Inevitable
Normal cognition, merosin positive	
Ullrich MDC	
Early spine rigidity	Inevitable
Associated mental abnormality	
Fukuyama	
Muscle–eye–brain	Inevitable, early onset
Walker–Warburg	

AMD, acid maltase deficiency; BMD, Becker muscular dystrophy; DM, distal myopathy; DM1, myotonic dystrophy; EDMD, Emery–Dreifuss muscular dystrophy; FSH, facioscapulohumeral dystrophy; LGMD 1, autosomal dominant limb-girdle muscular dystrophy; LGMD 2, autosomal recessive limb-girdle muscular dystrophy; MDC, congenital muscular dystrophy; OPMD, oculopharyngeal muscular dystrophy.

initial presentation, there would be a baseline to work from. The frequency would depend on how quickly their respiratory function was expected to decline—that is, annually in stable patients and more often in those with inevitable respiratory involvement. Spirometry is simple to carry out and is useful in monitoring the progression of respiratory muscle weakness. Other helpful investigations include mouth pressures, sniff nasal pressure, peak cough flow measurement and overnight oximetry.

The approach to the management of respiratory problems in muscle disease is multidisciplinary. Respiratory physiotherapy using manually assisted and mechanically assisted techniques is effective in clearing airways and improving peak cough flows in the event of chest infections. Once alveolar hypoventilation is identified in patients, NIV should be considered. Although there has never been a randomised controlled trial of NIV in muscle disorders, many studies have shown the positive effects NIV has on improving survival and quality of life.[17 116 117] General health measures such as prophylactic antibiotics, influenza vaccination and optimising the nutritional status of patients are also advocated.

It is important to keep both patients and their carers well informed about their condition. This allows them to understand the natural respiratory progression of their condition, to recognise the early signs and symptoms of chest infections, and be aware of the treatment modalities available to them, including the risks, benefits and complications associated with these measures, before finally making an informed decision regarding their respiratory care.

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